



= SOLID SUPPORT

R = TERMINAL PROTECTING GROUP FOR EXAMPLE: DIMETHOXYTRITYL (DMT)

(1) = CLEAVABLE LINKER

(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR

(2) ÎNVERTED DEOXYABASIC SUCCINATE)

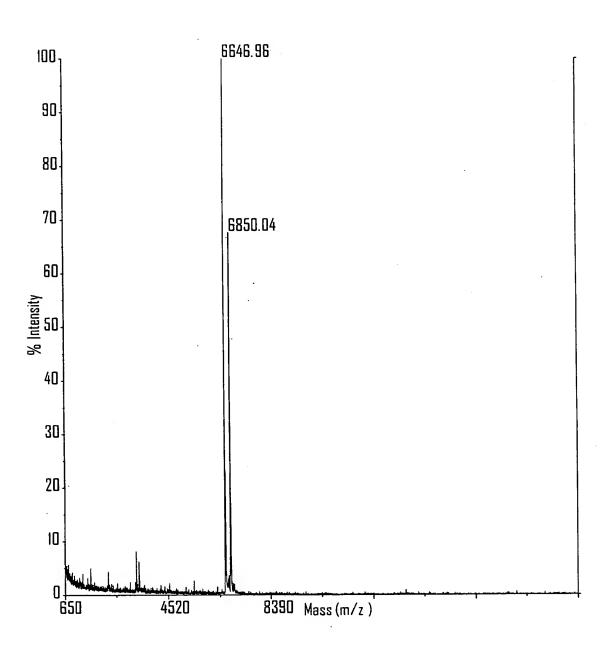
= CLEAVABLE LINKER

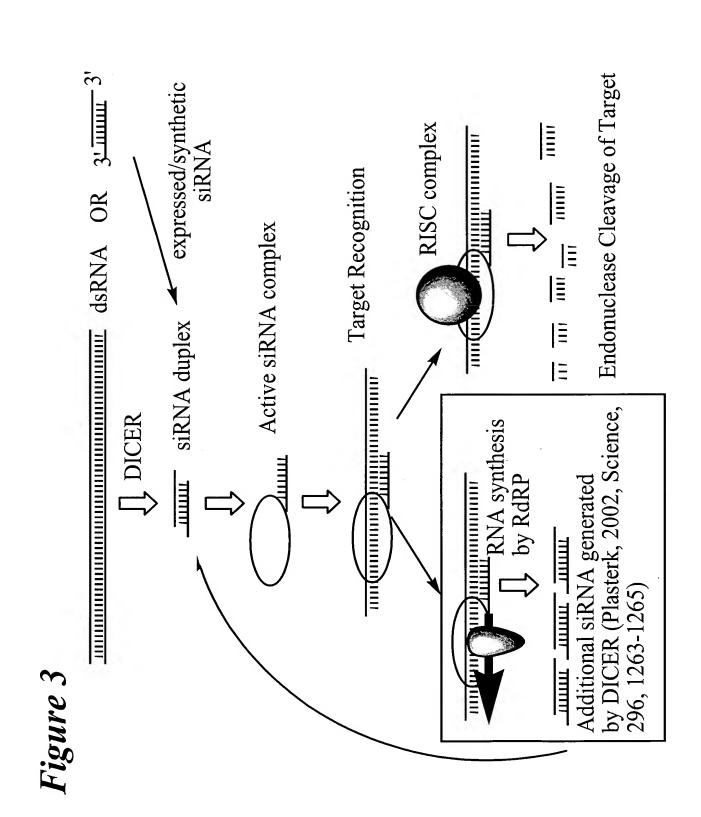
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR INVERTED DEOXYABASIC SUCCINATE)

INVERTED DEOXYABASIC SUCCINATE LINKAGE

**GLYCERYL SUCCINATE LINKAGE** 

Figure 2





			_
<b>A</b>		SENSE STRAND (SEQ ID NO 55) ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N)	)
	5'-	В-N N N N N N N N N N N N N N N N N N (N N)-В	-3'
A	<b>\[ 3'-</b>	$L\text{-}(N_sN)\ N\ N\$	-5'
		ANTISENSE STRAND (SEQ ID NO 56) ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N)	J
_	ALI	SENSE STRAND (SEQ ID NO 57) L PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-OM EXCEPT POSITIONS (N	(N )
	5'-	N N N N N N N N N N N N N N N N N N N	-3'
B	₹ 3'-	L-(N <sub>s</sub> N) N N N N N N N N N N N N N N N N N N	-5'
	ALL	ANTISENSE STRAND (SEQ ID NO 58) PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (	(N N)
	Ċ	GENIGE CER AND (GEO ID NO 50)	)
C		SENSE STRAND (SEQ ID NO 59) ALL PYRIMIDINES = 2'-O-ME OR 2'-FLUORO EXCEPT POSITIONS (N N)	
	∫ 5'-	B-N N N N N N N N N N N N N N N N N N N	-3'
	3'-	L-(N <sub>s</sub> N) N N N N N N N N N N N N N N N N N N	-5'
		ANTISENSE STRAND (SEQ ID NO 60) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) .	J
D	ALL F	SENSE STRAND (SEQ ID NO 61) PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DE	EOXY
	5'-	B-N N N N N N N N N N N N N N N N N N (N N)-B	-3'
U	<b>\</b> 3'-	$L$ -( $N_s$ N) NNNNNNNNNNNNNNNNNN	-5'
	ALL	ANTISENSE STRAND (SEQ ID NO 58) PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (	(N N)
E		SENSE STRAND (SEQ ID NO 62) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N)	)
	5'-	B-N N N N N N N N N N N N N N N N N N N	-3'
	<b>خ ک</b> ا۔	L-(N <sub>s</sub> N) N N N N N N N N N N N N N N N N N N	-5' >
	ALL	ANTISENSE STRAND (SEQ ID NO 58) PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (	(N N
F		SENSE STRAND (SEQ ID NO 61)	)
		YRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DE	
	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	B-N N N N N N N N N N N N N N N N N N N	-3'
	3'-	L-(N <sub>s</sub> N) N N N N N N N N N N N N N N N N N N	-5'
	1	ANTISENSE STRAND (SEO ID NO 63)	
	ALL P	ANTISENSE STRAND (SEQ ID NO 63) YRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEC	oxy

POSITIONS (NN) CAN COMPRISE ANY NUCLEOTIDE, SUCH AS DEOXYNUCLEOTIDES (eg. THYMIDINE) OR UNIVERSAL BASES
B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP

THAT IS OPTIONALLY PRESENT

L = GLYCERYL or B THAT IS OPTIONALLY PRESENT S = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE that is optionally absent

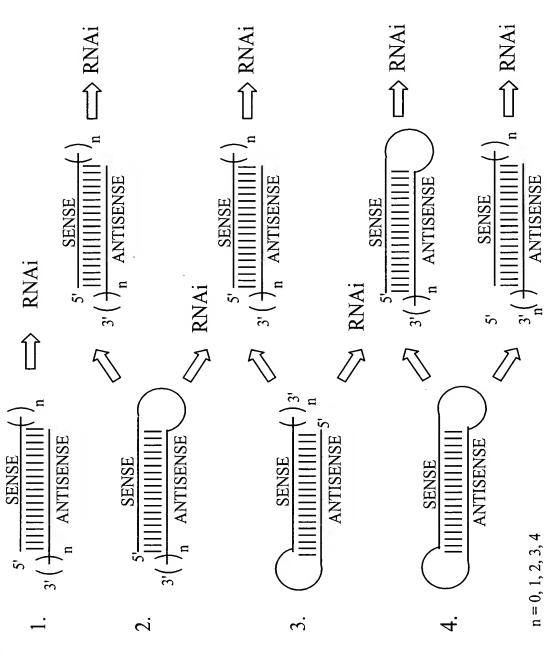
		SENSE STRAND (SEQ ID NO 64)	
A	5'-	iB-UCUGAUGAUGUCAGAUAUG <i>TT</i> -iB	-3'
	\\ 3'_	L- $T$ <sub>S</sub> $T$ A G A C U A C U A C A G U C U A U A C	-5'
		ANTISENSE STRAND (SEQ ID NO 65)	-5
		ANTISENSE STRAND (SEQ ID NO 03)	
		SENSE STRAND (SEQ ID NO 66)	7
В	5'-	u c u g <u>a</u> u g <u>a</u> u g u c <u>a g a</u> u <u>a</u> u g T <sub>S</sub> T	-3'
	√ 3'-	$L-T_ST$ $\underline{a}$ $\underline{g}$ $\underline{a}$ $\underline{c}$ $\underline{u}$ $\underline{a}$ $\underline{c}$ $\underline{a}$ $\underline{g}$ $\underline{u}$ $\underline{c}$ $\underline{u}$ $\underline{a}$ $\underline{u}$ $\underline{a}$ $\underline{c}$	-5' >
		ANTISENSE STRAND (SEQ ID NO 67)	
		THITIDENED STRIKE (SEQ ID 110 07)	
	Ĺ		ر
		SENSE STRAND (SEQ ID NO 68)	
	5,	'D	21
$\boldsymbol{C}$	3-	iB-u c u G A u G A u G u c A G A u A u G T T-iB	-3'
	) 3'-	L-T <sub>S</sub> T A G A c u A c u A c A G u c u A u A c	-5' }
		ANTISENSE STRAND (SEQ ID NO 69)	
			J
	Ĉ		ń
		SENSE STRAND (SEQ ID NO 70)	
Т	5'-	iB-u c u G A u G A u G u c A G A u A u G T T-iB	-3'
D	<b>خ</b> 3'-	L-T <sub>S</sub> T <u>a g a c u a c u a c a g u c u a u a c</u>	-5'
		ANTISENSE STRAND (SEQ ID NO 67)	
	7	SENSE STRAND (SEQ ID NO 71)	Ź
10	5'-	iB-u c u G A u G A u G u c A G A u A u G T T-iB	-3'
$\mathbf{E}$	₹ 3'-	L-T <sub>S</sub> T <u>a</u> g <u>a</u> c u <u>a</u> c u <u>a</u> c <u>a</u> g u c u <u>a</u> u <u>a</u> c	-5' >
		ANTISENSE STRAND (SEQ ID NO 67)	
			$\prec$
		SENSE STRAND (SEQ ID NO 70)	
	5'-	iB-u c u G A u G A u G u c A G A u A u G T T-iB	-3'
${f F}$	∫ 5'-	L-T <sub>S</sub> TAGAcuAcuAcAGucuAuAc	-5'
_		ANTISENSE STRAND (SEQ ID NO 72)	
		111110L10L 0110110 (0LQ ID 110 12)	
			J

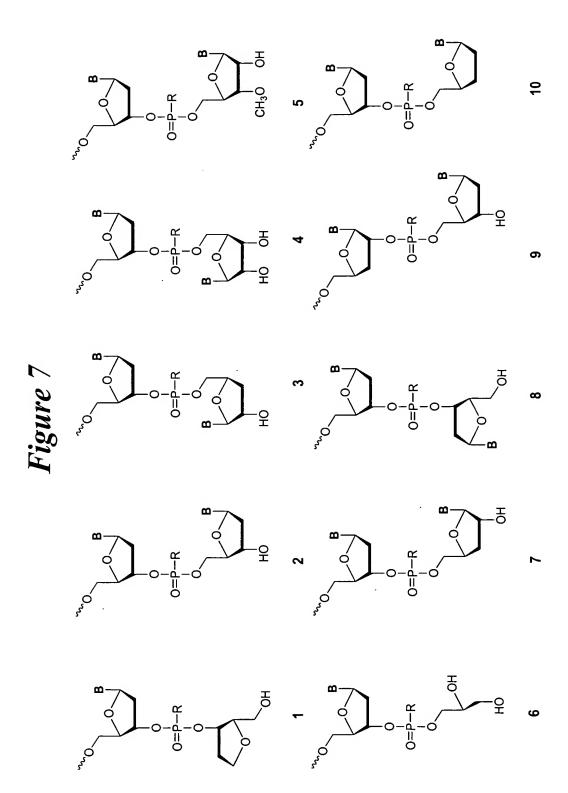
lower case = 2'-O-Methyl or 2'-deoxy-2'-fluoro

italic lower case = 2'-deoxy-2'-fluoro

underline = 2'-O-methyl

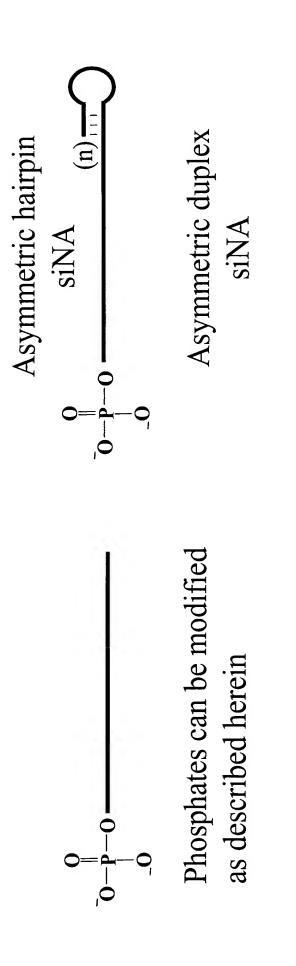
ITALIC UPPER CASE = DEOXY
iB = INVERTED DEOXYABASIC
L = GLYCERYL MOIETY or iB OPTIONALLY PRESENT
S = PHOSPHOROTHIOATE OR
PHOSPHORODITHIOATE OPTIONALLY PRESENT

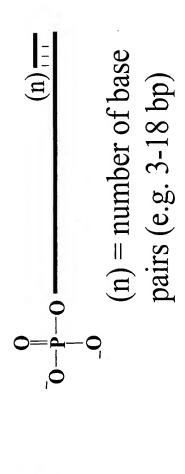




R = O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, or aralkyl B = Independently any nucleotide base, either naturally occurring or chemically modified, or optionally H (abasic).

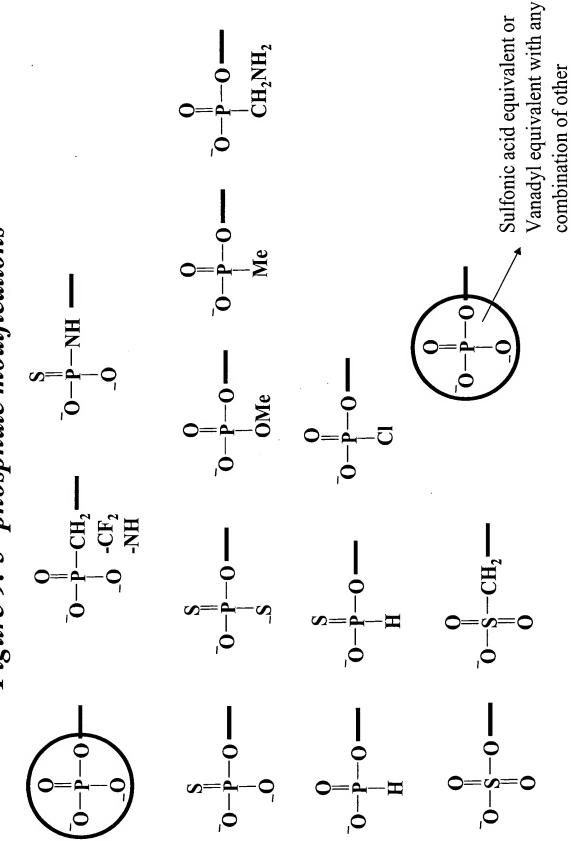
# Figure 8: Phosphorylated siNA constructs





modifications herein

# Figure 9: 5'-phosphate modifications



# Figure 10A: Duplex forming oligonucleotide constructs that utilize palindrome

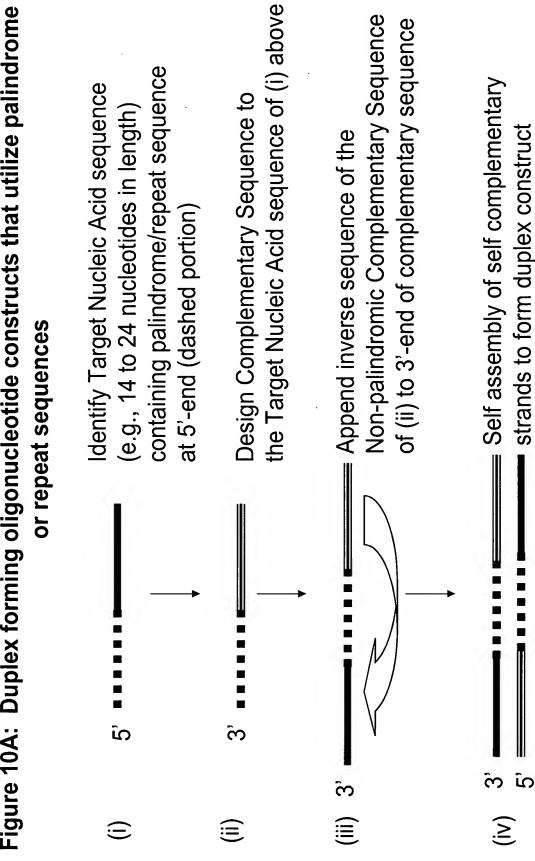
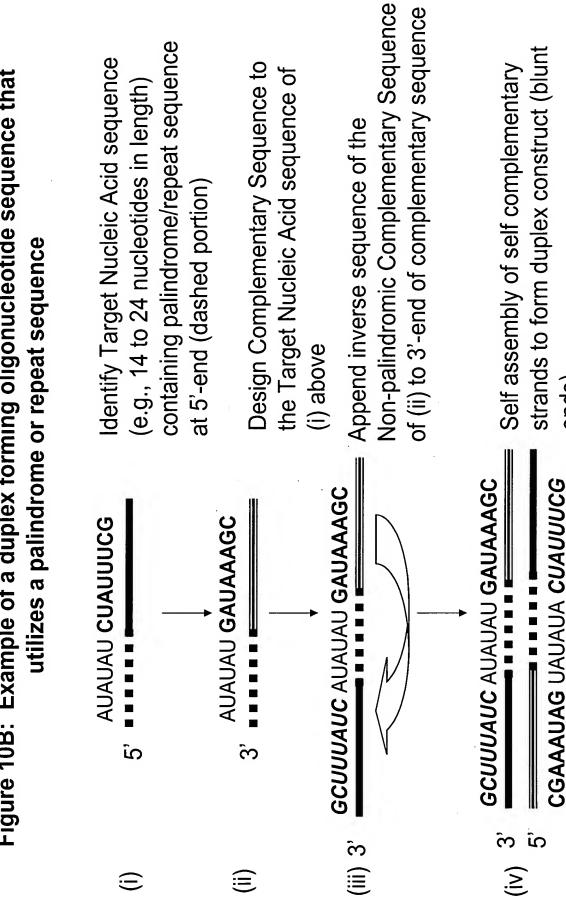


Figure 10B: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence



ends)

Figure 10C: Example of a duplex forming oligonucleotide sequence that

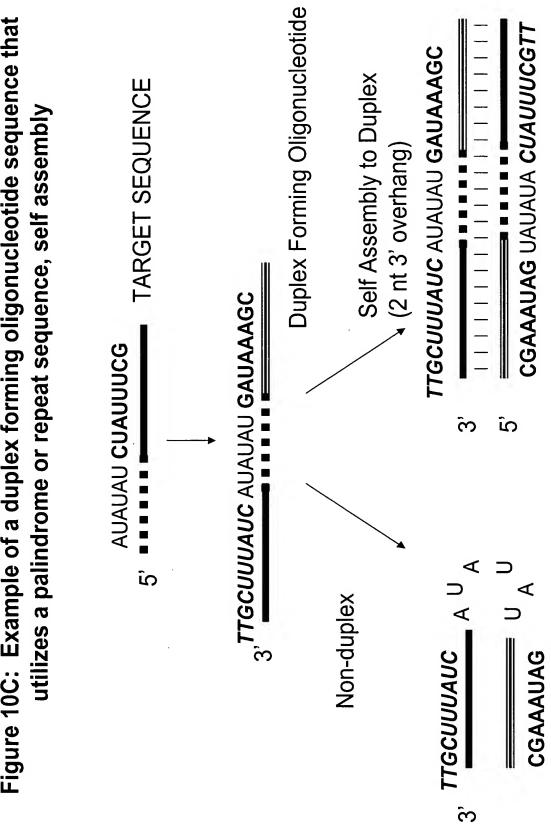
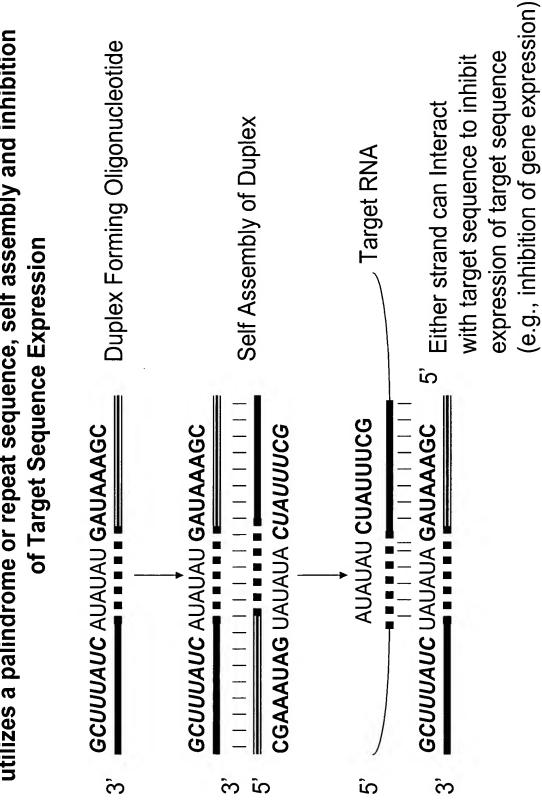


Figure 10D: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly and inhibition



## Figure 11: Duplex forming oligonucleotide constructs that utilize artificial palindrome or repeat sequences

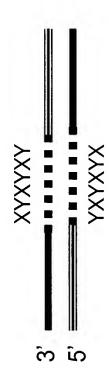
Identify Target Nucleic Acid sequence (e.g., 14 to 24 nucleotides in length)

ΩÎ

Design Complementary Sequence and utilize modified nucleotides (shown as X, Y) that interact with a portion of the target sequence and result in the formation of a palindrome/repeat sequence (e.g., 2 to 12 nucleotides) at 3'-end (dashed portion)

Append inverse sequence of Complementary region to 3'-end of palindrome/repeat sequence

XXXXX



Hybridize self complementary strands to form duplex siNA construct

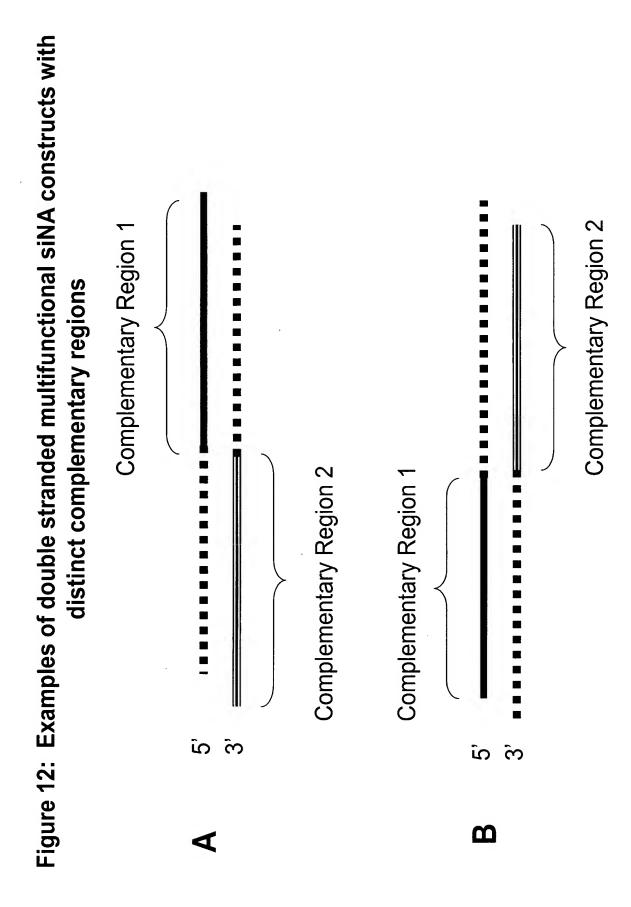


Figure 13: Examples of hairpin multifunctional siNA constructs with Complementary Region 1 Complementary Region 2 distinct complementary regions Complementary Region 2 Complementary Region 1 က် က်  $\hat{\Omega}$ ŝ മ

Figure 14: Examples of double stranded multifunctional siNA constructs with

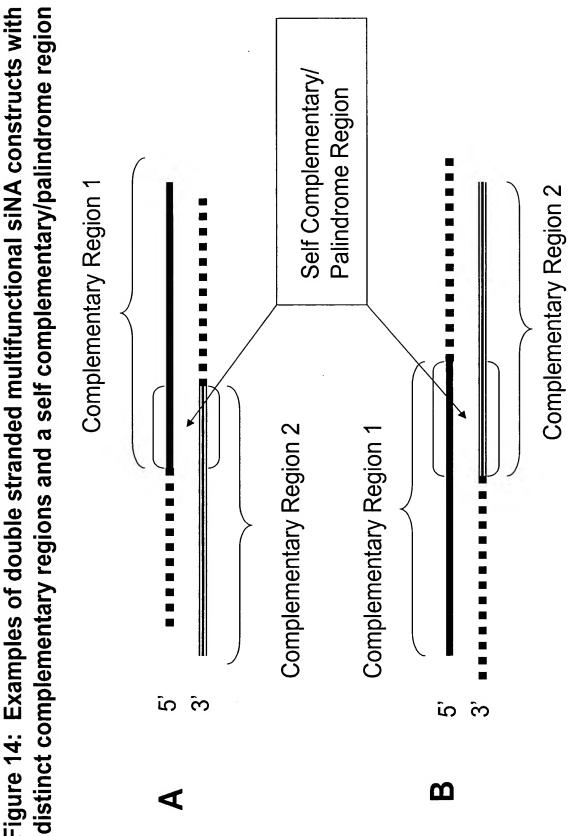
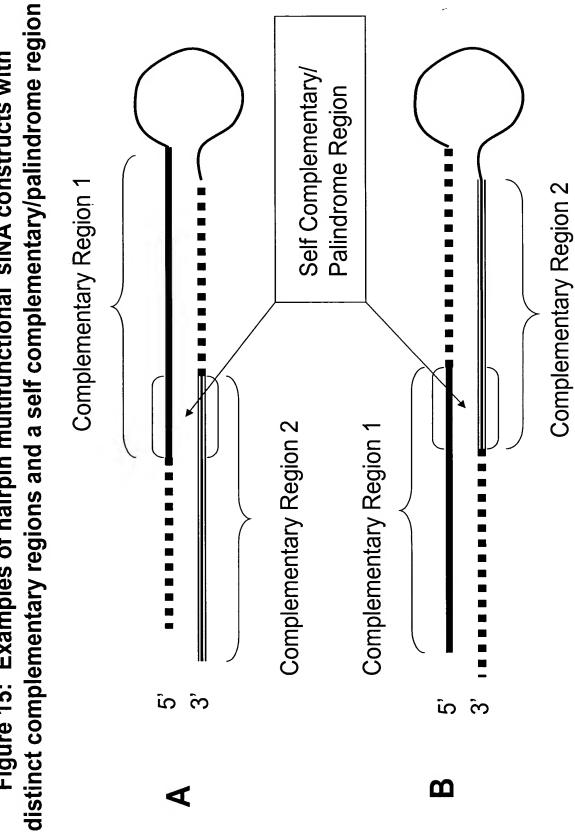


Figure 15: Examples of hairpin multifunctional siNA constructs with



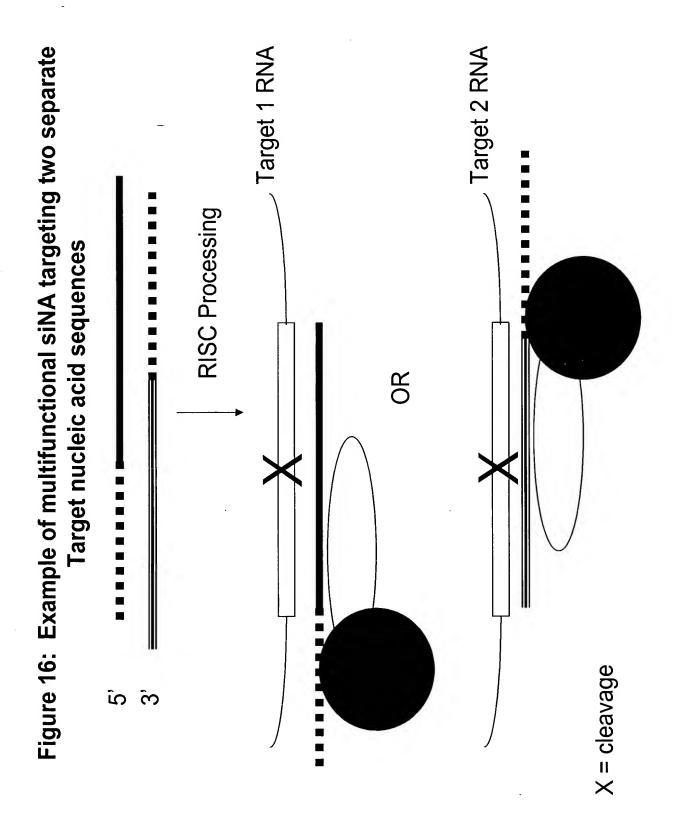
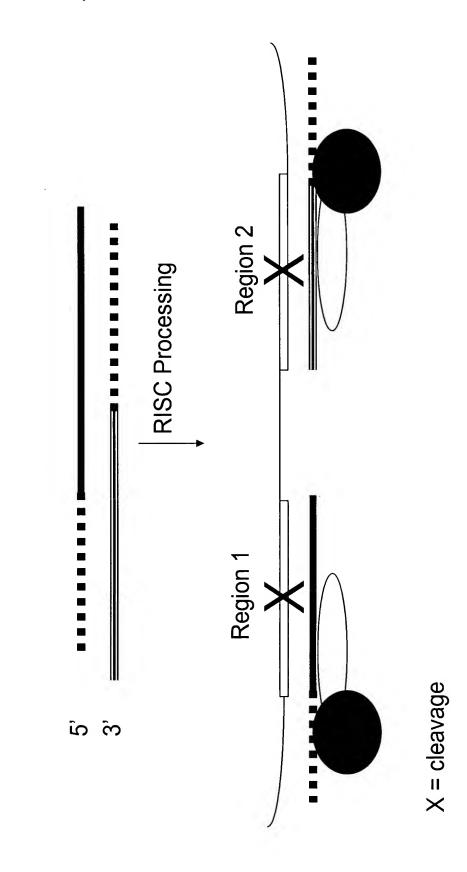
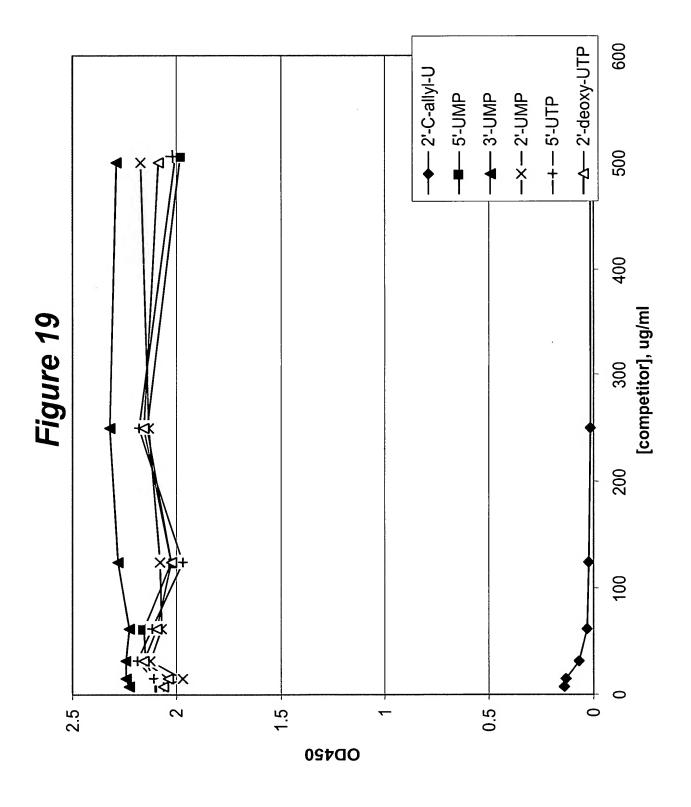


Figure 17: Example of multifunctional siNA targeting two regions within the same target nucleic acid sequence

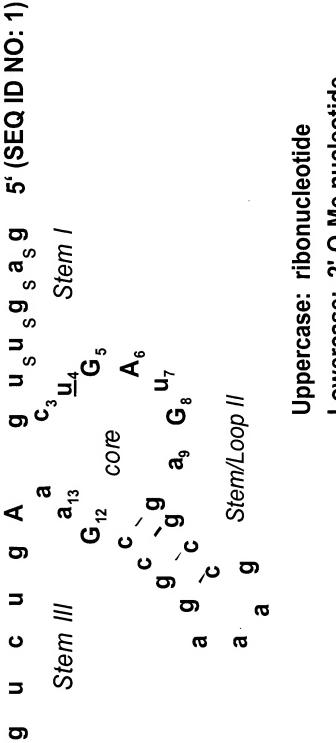






 $\mathbf{\omega}$ 

3



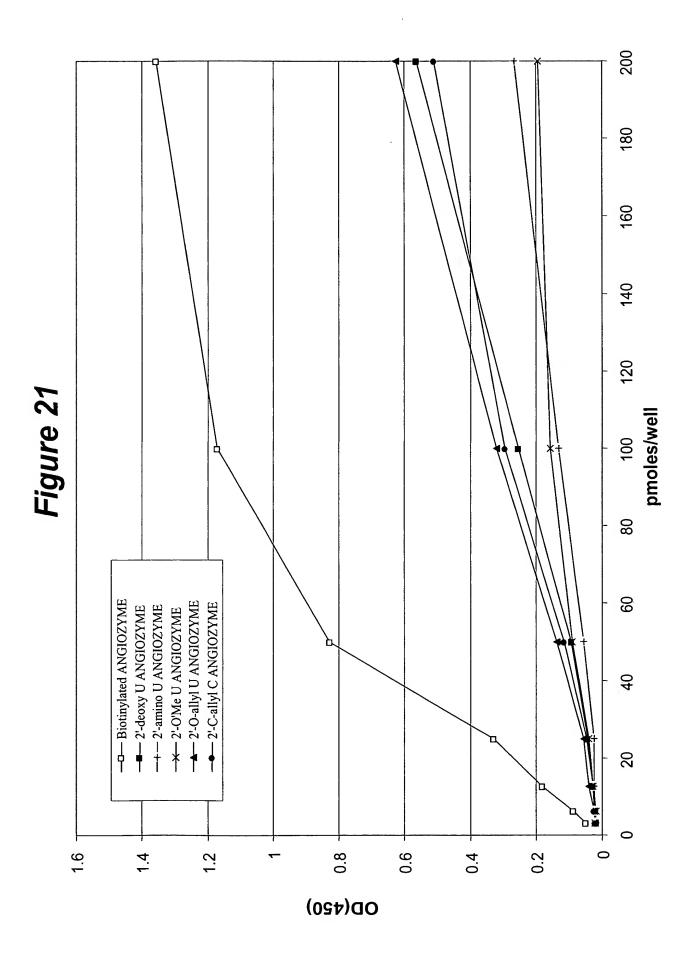
Lowercase: 2'-O-Me nucleotide

<u>U</u>: 2'-deoxy-2'-C-allyl Uridine

**ANGIOZYMETM** 

B: inverted 2'-deoxyribose abasic

S: phosphorothioate linkage



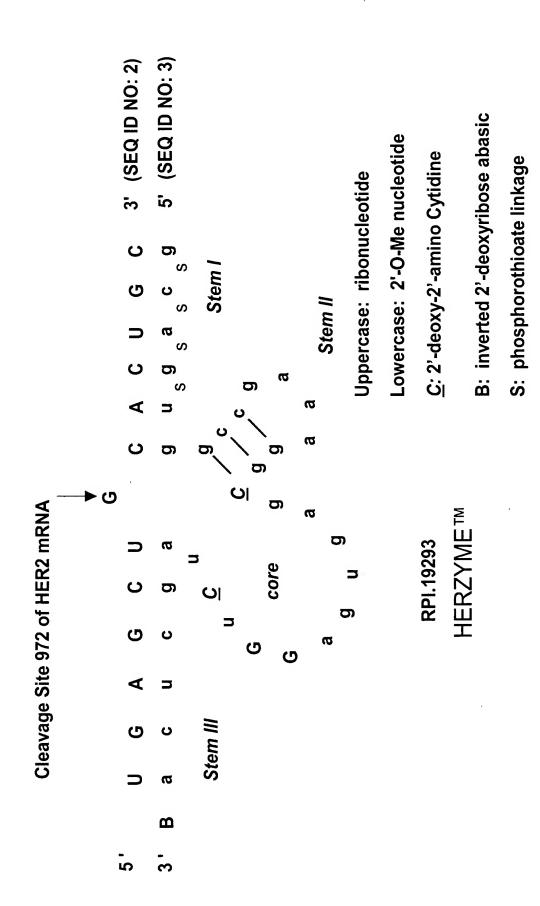


Figure 23

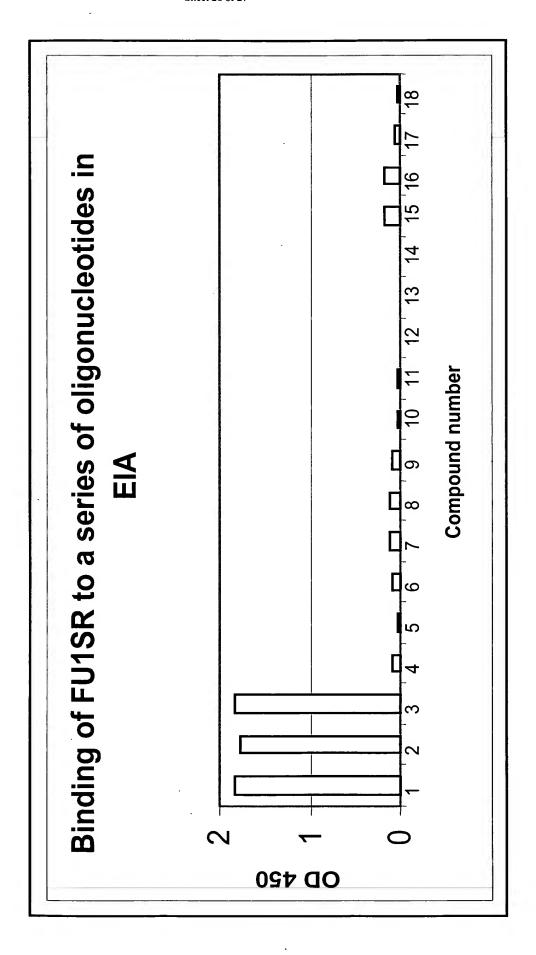


Figure 24

